

Supplemental Online Content

Momozawa Y, Sasai R, Usui Y, et al. Expansion of cancer risk profile for *BRCA1* and *BRCA2* pathogenic variants. *JAMA Oncology*. Published online April 14, 2022. doi:10.1001/jamaoncol.2022.0476

eAppendix.

eFigure 1. Overall procedure for this study

eFigure 2. Location and the number of pathogenic variants in *BRCA1* and *BRCA2* in patients

eFigure 3. Distribution of carrier frequency in patients between seven regions of Japan in (A) *BRCA1* and (B) *BRCA2*

eFigure 4. Carrier frequency in patients with multiple cancer diagnoses, for the 14 cancer types

eFigure 5. Comparison of the carrier frequency of the 14 cancer types and controls between females and males in (A) *BRCA1* and (B) *BRCA2*

eFigure 6. The proportion of patients with pathogenic variants by the age at diagnosis of each cancer type in 10-year age groupings

eFigure 7. Associations between carrier status of pathogenic variants in *BRCA1* or *BRCA2* and family history

eFigure 8. The combined *BRCA1* or *BRCA2* carrier frequency of patients according to family history of the seven cancer types

eTable 1. List of the 315 pathogenic variants in *BRCA1* and *BRCA2*

eTable 2. Comparison of *BRCA1* and *BRCA2* pathogenic variant frequency for all* patients for each cancer type, versus controls

eTable 3. Results of two sensitivity analyses in breast cancer

eTable 4. Mean age at diagnosis of each cancer type in patients with or without pathogenic variants in *BRCA1* and *BRCA2*

eTable 5. Comparisons of histological subtypes between carriers with pathogenic variants and non-carriers

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix.

1. Assignment of clinical significance for all variants

We assigned clinical significance (pathogenic, likely pathogenic, benign, likely benign or uncertain) for all variants using *BRCA1/2* variant classification criteria (https://variansci.files.wordpress.com/2018/10/enigma-brca12-gene-variant-classification-criteria_v2-5-1.pdf) previously developed by members of the ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) consortium¹, in their role as a ClinGen-approved external expert panel for *BRCA1/2*. Pathogenic and likely pathogenic variants were collectively referred to as pathogenic variants in this study.

2. Calculation for the lifetime cumulative risk of each cancer type

We estimated the cumulative risk for each cancer by using the odds ratio of each category, the prevalence of each category among our study control, the age-specific cancer incidence rate of Japan², and the age-specific population rate of Japan in 2017². We assumed that the site-specific prevalence of each category was the same in each age group since the presence or absence of the pathogenic variants did not change after birth, and also assumed that the distribution of the pathogenic variants for each cancer in the Japanese general population was represented by that in our study control sample³⁻⁵.

Genetic analysis

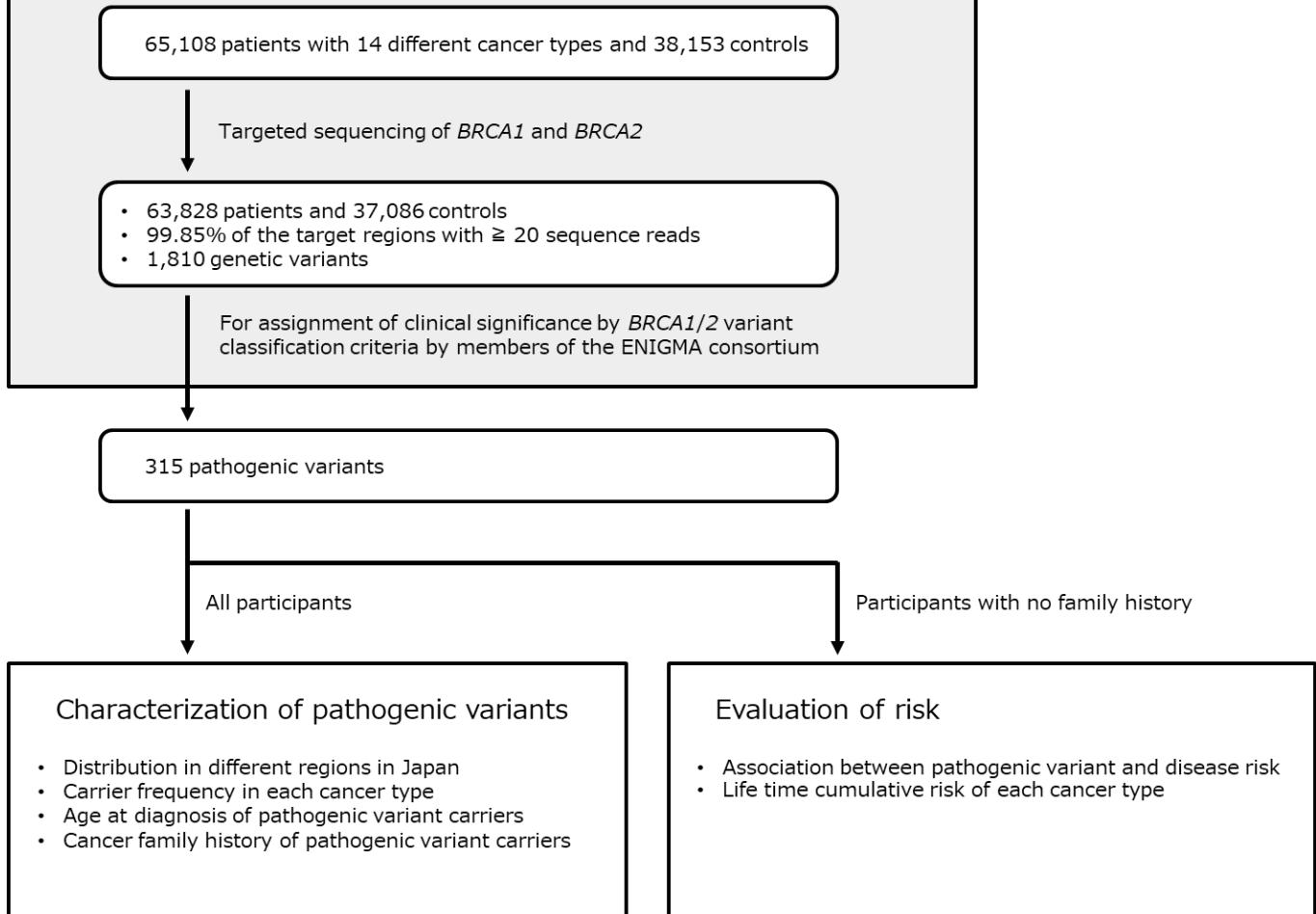
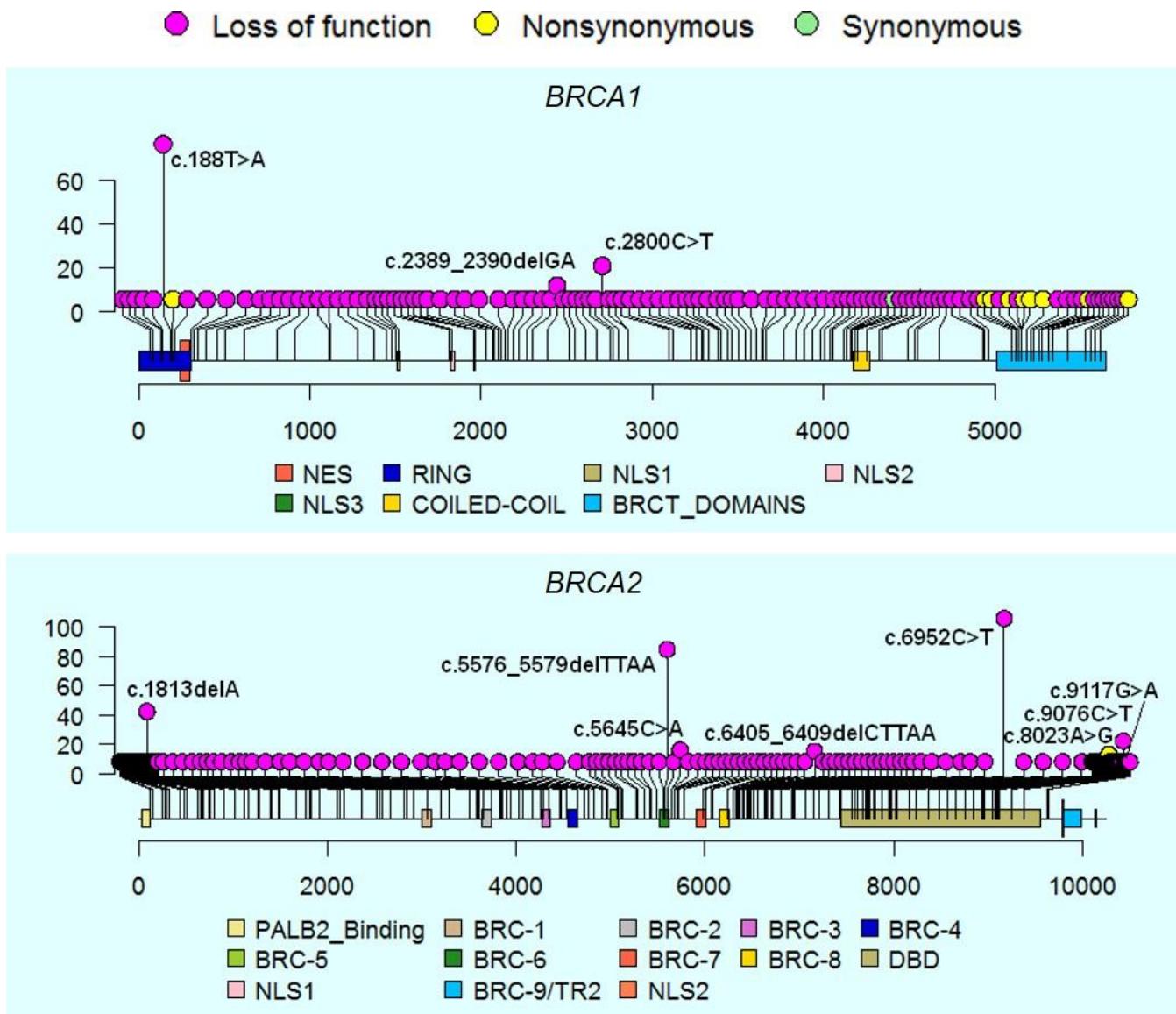
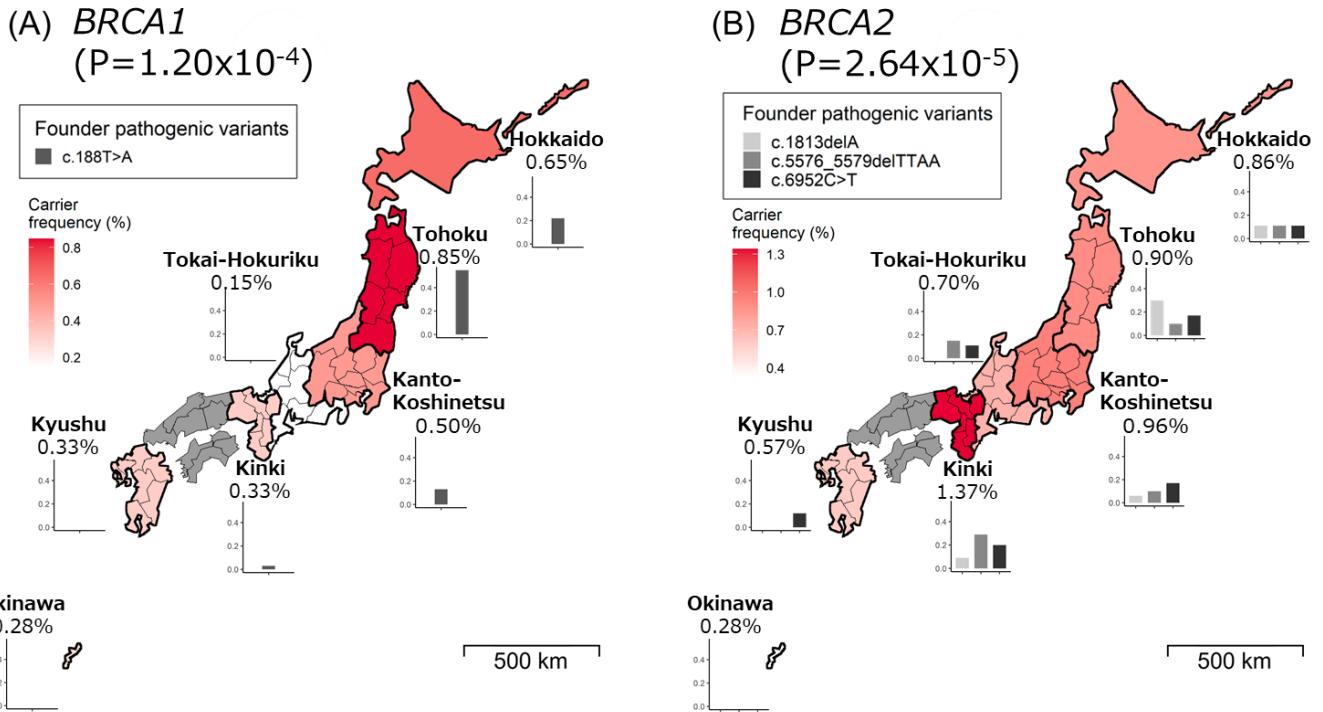


Figure 1. Overall procedure for this study



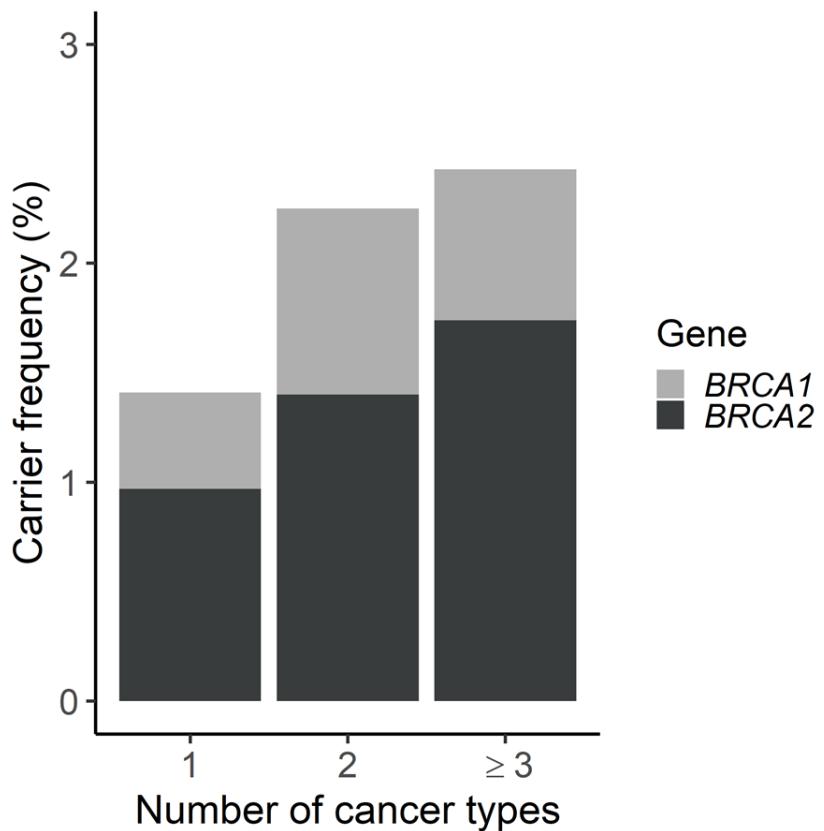
eFigure 2. Location and the number of pathogenic variants in *BRCA1* and *BRCA2* in patients.

Locations of pathogenic variants found in patients and protein domains are shown by lollipop structures with the variant type indicated by color. Protein domains designated in the ENIGMA *BRCA1/2* gene variant classification criteria (eAppendix 1) are described. HGVS.c of frequent variants with ≥ 10 patients is shown. Three pathogenic variants were shared in ≥ 10 patients in *BRCA1* (c.188T>A in 78 patients, c.2389_2390delGA in 14 patients, and c.2800C>T in 23 patients), and eight pathogenic variants for *BRCA2* (c.1813delA in 45 patients, c.5576_5579delTTAA in 87 patients, c.5645C>A in 19 patients, c.6405_6409delCTTAA in 18 patients, c.6952C>T in 108 patients, c.8023A>G in 16 patients, c.9076C>T in 25 patients, and c.9117G>A in 10 patients).



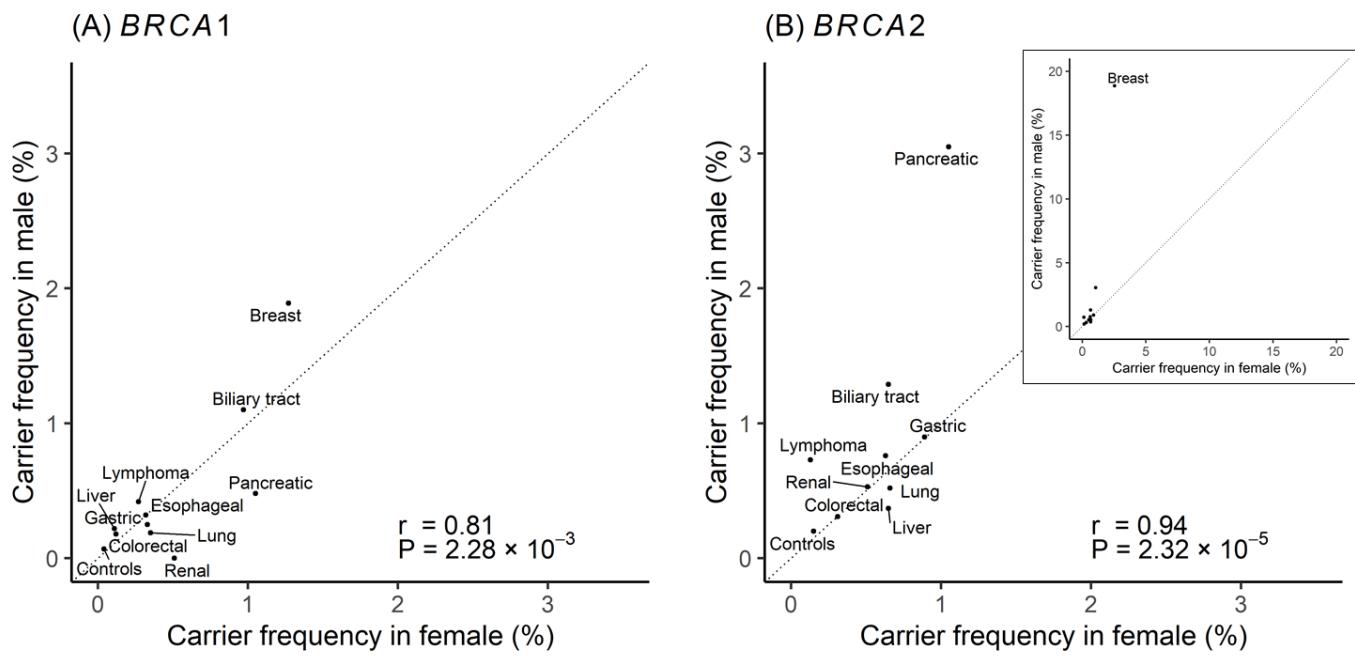
eFigure 3. Distribution of carrier frequency in patients between seven regions of Japan in (A) *BRCA1* and (B) *BRCA2*.

The carrier frequency is shown as a heat map between white and red. P value was calculated by χ^2 test. Grey shows the region in which we did not analyze the samples. In each region, the region name, frequency of pathogenic variants, the histogram for the frequency of one (c.188T>A) in *BRCA1* or three founder pathogenic variants (c.1813delA, c.5576_5579delTTAA, and c.6952C>T) in *BRCA2* are shown. Regional differences could be largely explained by the different proportion of founder pathogenic variants (shown as histograms). *BRCA1* c.188T>A was observed in 0.55% of patients from Tohoku, but was absent from patients from Tokai-Hokuriku. The total proportion of the three top founder *BRCA2* pathogenic variants (c.1813delA, c.5576_5579delTTAA, and c.6952C>T) ranged from 0.58% in Kinki to 0% in Okinawa.



eFigure 4. Carrier frequency in patients with multiple cancer diagnoses, for the 14 cancer types.

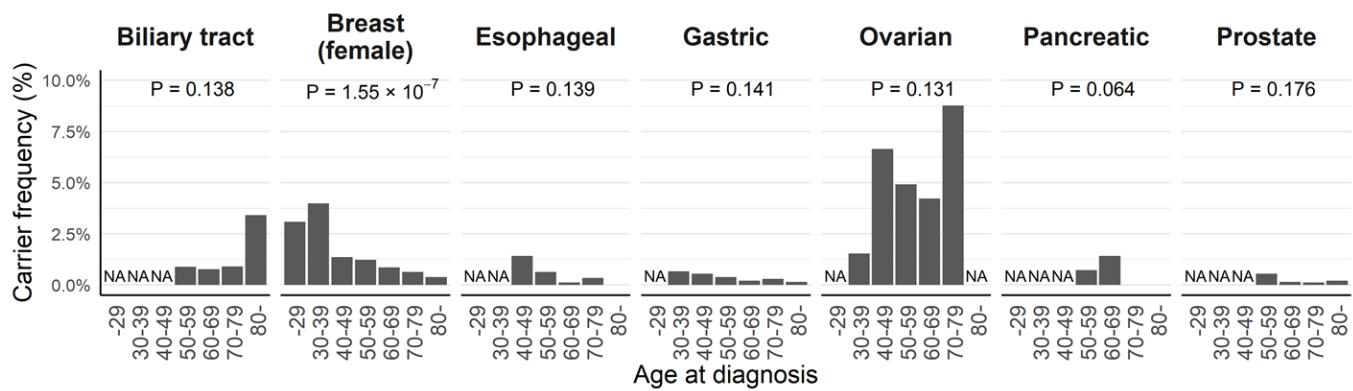
For both genes, carrier frequency significantly increased according to the number of cancer types diagnosed for a patient ($P = 7.73 \times 10^{-4}$ in *BRCA1* and $P = 4.90 \times 10^{-3}$ in *BRCA2* by the Cochran-Armitage test).



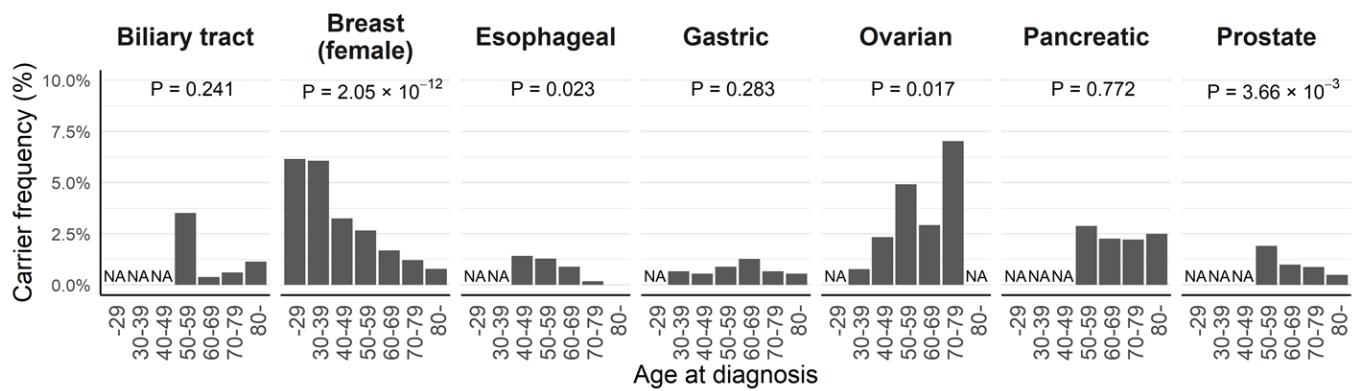
eFigure 5. Comparison of the carrier frequency of the 14 cancer types and controls between females and males in (A) BRCA1 and (B) BRCA2.

Carrier frequency for females and males in each cancer type was significantly correlated. The high carrier frequency of pathogenic variants in BRCA2 is comparable to that of other populations⁶.

(A) *BRCA1*



(B) *BRCA2*



eFigure 6. The proportion of patients with pathogenic variants by the age at diagnosis of each cancer type in 10-year age groupings.

Data are shown in the 10-year age groups with 50 or more patients. The P value was calculated using the Cochran-Armitage test to test for a linear association. $P = 7.14 \times 10^{-3}$ was set at the threshold of significance.

(A) *BRCA1*

		Family history						
		Biliary tract	Breast	Esophageal	Gastric	Ovarian	Pancreatic	Prostate
Patient cancer type	Biliary tract	4.9 (0.1 - 39.3) 0.211	5.2 (0.5 - 28.2) 0.081	5.1 (0.1 - 41.5) 0.202	0.4 (0.0 - 3.4) 0.692	0.0 (0.0 - 115.3) 1.000	3.0 (0.1 - 23.2) 0.316	0.0 (0.0 - 26.8) 1.000
	Breast (female)	1.0 (0.1 - 3.9) 0.722	3.9 (2.6 - 5.8) 1.05×10^{-10}	1.1 (0.3 - 3.0) 0.784	1.4 (0.9 - 2.2) 0.075	10.1 (5.2 - 18.3) 1.30×10^{-9}	1.1 (0.3 - 2.6) 0.809	0.4 (0.0 - 1.5) 0.244
	Esophageal	11.0 (0.2 - 95.3) 0.102	8.4 (0.8 - 52.1) 0.038	2.6 (0.1 - 21.3) 0.358	0.6 (0.0 - 5.4) 1.000	44.2 (0.9 - 435.4) 0.029	0.0 (0.0 - 17.0) 1.000	0.0 (0.0 - 28.9) 1.000
	Gastric	5.9 (0.7 - 23.8) 0.051	5.3 (1.8 - 13.5) 2.01×10^{-3}	0.0 (0.0 - 4.0) 1.000	0.8 (0.3 - 2.0) 0.836	11.1 (1.3 - 45.7) 0.016	1.0 (0.0 - 6.2) 1.000	0.0 (0.0 - 6.3) 1.000
	Ovarian	3.8 (0.7 - 13.7) 0.061	2.7 (1.3 - 5.4) 4.49×10^{-3}	1.9 (0.4 - 6.4) 0.227	1.1 (0.6 - 2.0) 0.761	14.5 (7.3 - 28.2) 3.17×10^{-13}	1.4 (0.4 - 4.1) 0.528	0.0 (0.0 - 1.7) 0.166
	Pancreatic	0.0 (0.0 - 38.2) 1.000	2.6 (0.1 - 21.5) 0.361	0.0 (0.0 - 19.8) 1.000	0.0 (0.0 - 2.4) 0.360	75.9 (5.9 - 649.8) 8.63×10^{-4}	0.0 (0.0 - 8.2) 1.000	0.0 (0.0 - 20.4) 1.000
	Prostate	0.0 (0.0 - 19.0) 1.000	3.9 (0.7 - 13.8) 0.055	0.0 (0.0 - 8.8) 1.000	1.8 (0.5 - 5.3) 0.350	29.9 (3.2 - 133.4) 2.68×10^{-3}	1.6 (0.0 - 10.2) 0.481	1.4 (0.2 - 6.0) 0.655

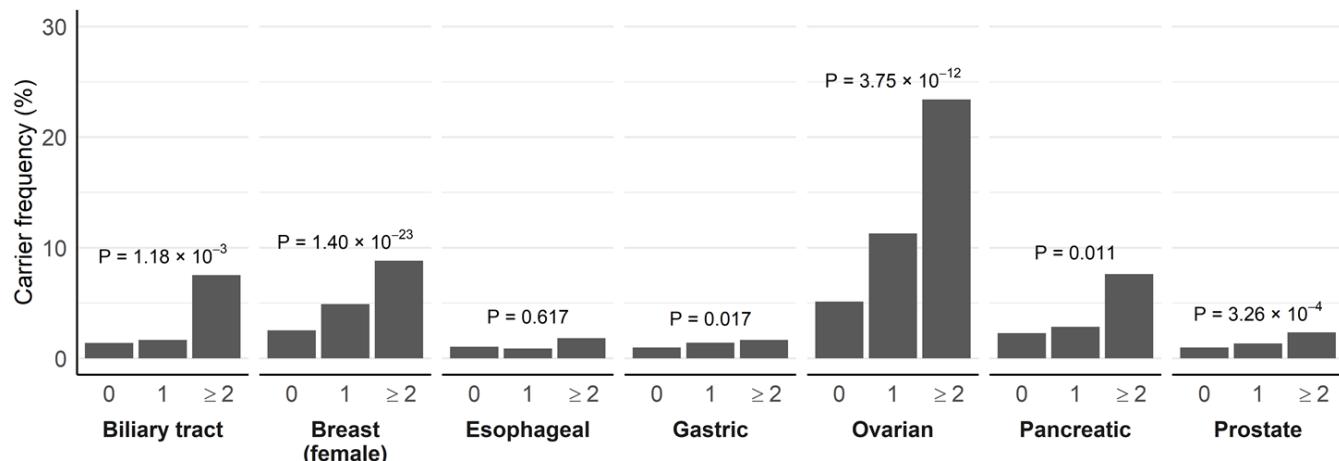
(B) *BRCA2*

		Family history						
		Biliary tract	Breast	Esophageal	Gastric	Ovarian	Pancreatic	Prostate
Patient cancer type	Biliary tract	0.0 (0.0 - 20.2) 1.000	15.1 (2.9 - 73.1) 7.71×10^{-4}	5.1 (0.1 - 41.5) 0.202	4.6 (1.0 - 23.4) 0.027	0.0 (0.0 - 115.3) 1.000	0.0 (0.0 - 12.2) 1.000	0.0 (0.0 - 26.8) 1.000
	Breast (female)	1.3 (0.4 - 3.2) 0.443	3.0 (2.2 - 4.0) 7.06×10^{-12}	1.6 (0.8 - 2.9) 0.172	1.3 (1.0 - 1.8) 0.068	3.6 (1.7 - 6.7) 5.81×10^{-4}	2.8 (1.7 - 4.3) 4.87×10^{-5}	1.9 (1.1 - 3.1) 0.019
	Esophageal	0.0 (0.0 - 17.5) 1.000	1.4 (0.0 - 9.2) 0.531	0.0 (0.0 - 4.0) 0.619	0.9 (0.2 - 3.3) 1.000	0.0 (0.0 - 74.1) 1.000	1.6 (0.0 - 10.8) 0.478	0.0 (0.0 - 10.8) 1.000
	Gastric	0.8 (0.0 - 4.8) 1.000	3.3 (1.7 - 5.9) 4.92×10^{-4}	1.0 (0.2 - 2.9) 1.000	1.2 (0.8 - 1.9) 0.359	6.8 (1.8 - 18.7) 3.88×10^{-3}	1.2 (0.3 - 3.3) 0.567	0.5 (0.0 - 2.8) 0.725
	Ovarian	0.0 (0.0 - 6.2) 1.000	3.8 (1.7 - 7.9) 6.96×10^{-4}	0.9 (0.0 - 5.3) 1.000	1.6 (0.8 - 3.1) 0.148	3.2 (0.9 - 8.4) 0.032	1.5 (0.3 - 5.0) 0.451	3.8 (1.1 - 10.3) 0.017
	Pancreatic	0.0 (0.0 - 9.6) 1.000	4.5 (1.3 - 13.1) 0.011	1.3 (0.0 - 8.3) 0.562	1.9 (0.7 - 4.8) 0.203	0.0 (0.0 - 31.1) 1.000	1.8 (0.3 - 6.2) 0.418	1.3 (0.0 - 8.6) 0.552
	Prostate	1.5 (0.2 - 5.7) 0.389	3.3 (1.8 - 5.7) 1.06×10^{-4}	0.7 (0.1 - 2.6) 1.000	0.8 (0.5 - 1.4) 0.536	0.0 (0.0 - 7.9) 1.000	4.3 (2.3 - 7.5) 1.01×10^{-5}	1.9 (1.0 - 3.2) 0.024

OR (95%CI)
P value

eFigure 7. Associations between carrier status of pathogenic variants in *BRCA1* or *BRCA2* and family history.

Fisher's exact test was used. $P =$ was 1.02×10^{-3} considered as the threshold of significance by the Bonferroni correction. Red indicates $P < 1.02 \times 10^{-3}$, and deep red shows $OR \geq 4$ in addition to $P < 1.02 \times 10^{-3}$.



eFigure 8. The combined *BRCA1* or *BRCA2* carrier frequency of patients according to family history of the seven cancer types.

Carrier frequency with patients the seven associated cancer types was compared for individuals without family history on any of the seven cancer types versus those with reported family history of 1 cancer type, or with family history of ≥ 2 cancer types. The P value was calculated using the Cochran-Armitage test to test for a linear association. P = 7.14×10^{-3} was set at the threshold of significance. Calculations for male breast cancer were not done due to the low number of patients.

4. eTables

eTable 1. List of the 315 pathogenic variants in *BRCA1* and *BRCA2*

Chromosome	Position	Reference allele	Alternative allele	dbSNP151	Gene	Annotation	HGVSc	HGVSp	Carrier frequency in patients (%)	Carrier frequency in controls (%)	Call rate (%)	P value for Hardy-Weinberg equilibrium in controls	Average depth
1 3	32,893,26 9	CTATAA	C	.	<i>BRCA2</i>	frameshift variant	c.125_129delATAAT	p.Tyr42fs	0.002	0	100	1	2,069
1 3	32,893,29 1	G	T	rs80358435	<i>BRCA2</i>	stop gained	c.145G>T	p.Glu49*	0.002	0	100	1	2,948
1 3	32,893,39 3	G	T	rs886040428	<i>BRCA2</i>	stop gained	c.247G>T	p.Glu83*	0.002	0	100	1	2,796
1 3	32,893,42 0	C	T	rs80358529	<i>BRCA2</i>	stop gained	c.274C>T	p.Gln92*	0.002	0	100	1	878
1 3	32,893,42 5	TC	T	.	<i>BRCA2</i>	frameshift variant	c.281delC	p.Pro94fs	0.002	0	100	1	878
1 3	32,893,43 5	G	T	rs397507646	<i>BRCA2</i>	stop gained	c.289G>T	p.Glu97*	0.003	0	100	1	878
1 3	32,893,46 3	G	A	rs397507303	<i>BRCA2</i>	splice donor variant & intron variant	c.316+1G>A		0.002	0	100	1	878
1 3	32,893,46 4	T	C	rs81002805	<i>BRCA2</i>	splice donor variant & intron variant	c.316+2T>C		0.005	0.003	100	1	878
1 3	32,900,25 1	C	T	rs397507717	<i>BRCA2</i>	stop gained	c.439C>T	p.Gln147*	0.002	0	100	1	1,221

1 3	32,900,28 8	G	A	rs81002797	<i>BRCA2</i>	splice donor variant & intron variant	c.475+1G>A		0.013	0	100	1	1,222
1 3	32,900,38 6	T	A	.	<i>BRCA2</i>	stop gained	c.483T>A	p.Cys161*	0.002	0	100	1	1,980
1 3	32,900,42 1	T	C	.	<i>BRCA2</i>	splice donor variant & intron variant	c.516+2T>C		0.003	0	100	1	990
1 3	32,903,57 9	G	A	rs81002820	<i>BRCA2</i>	Splice acceptor variant & intron variant	c.632-1G>A		0.003	0	100	1	1,206
1 3	32,903,60 4	CTG	C	rs113169227 3; rs80359604	<i>BRCA2</i>	frameshift variant	c.658_659delGT	p.Val220fs	0.006	0	100	1	1,206
1 3	32,903,61 2	CCT	C	.	<i>BRCA2</i>	frameshift variant	c.666_667delTC	p.His223fs	0.002	0	100	1	1,206
1 3	32,905,05 5	G	T	.	<i>BRCA2</i>	splice acceptor variant & intron variant	c.682-1G>T		0.002	0	100	1	2,356
1 3	32,905,10 9	AT	A	.	<i>BRCA2</i>	frameshift variant	c.738delT	p.Phe246fs	0.002	0	100	1	2,357
1 3	32,905,12 3	TGACA	T	rs145570192 6; rs80359659	<i>BRCA2</i>	frameshift variant	c.755_758delACAG	p.Asp252fs	0.009	0	100	1	2,357
1 3	32,905,16 9	T	G	rs886040942	<i>BRCA2</i>	splice donor variant & intron variant	c.793+2T>G		0.002	0	100	1	1,177
1 3	32,906,41 0	AT	A	rs886040739	<i>BRCA2</i>	frameshift variant	c.798delT	p.Phe266fs	0.002	0	99.31 3	1	102
1 3	32,906,41 5	G	GA	rs886040744	<i>BRCA2</i>	frameshift variant	c.805dupA	p.Thr269fs	0.008	0	99.31 3	1	102
1 3	32,906,50 6	A	AAC	.	<i>BRCA2</i>	frameshift variant	c.893_894dupCA	p.Val299fs	0.002	0	99.98	1	169
1 3	32,906,62 7	GC	G	.	<i>BRCA2</i>	frameshift variant	c.1013delC	p.Ala338fs	0.003	0	99.99 7	1	477
1 3	32,906,73 7	GC	G	.	<i>BRCA2</i>	frameshift variant	c.1125delC	p.Phe376fs	0.002	0	100	1	672

1 3	32,906,76 9	AG	A	rs397507262	<i>BRCA2</i>	frameshift variant	c.1156delG	p.Glu386fs	0	0.003	100	1	825
1 3	32,906,77 3	AG	A	.	<i>BRCA2</i>	frameshift variant	c.1159delG	p.Val387fs	0.002	0	100	1	825
1 3	32,906,79 9	G	A	rs886040347	<i>BRCA2</i>	stop gained	c.1184G>A	p.Trp395*	0	0.003	100	1	825
1 3	32,906,87 6	C	T	rs80358419	<i>BRCA2</i>	stop gained	c.1261C>T	p.Gln421*	0.002	0.003	100	1	831
1 3	32,906,88 8	GA	G	rs80359274	<i>BRCA2</i>	frameshift variant	c.1278delA	p.Asp427fs	0.014	0	100	1	831
1 3	32,907,00 3	CAG	C	rs80359283	<i>BRCA2</i>	frameshift variant	c.1389_1390delAG	p.Val464fs	0.003	0	100	1	440
1 3	32,907,01 4	A	T	rs80358427	<i>BRCA2</i>	stop gained	c.1399A>T	p.Lys467*	0.006	0.003	100	1	440
1 3	32,907,02 6	G	T	rs80358428	<i>BRCA2</i>	stop gained	c.1411G>T	p.Glu471*	0.002	0	100	1	440
1 3	32,907,09 5	GT	G	.	<i>BRCA2</i>	frameshift variant	c.1481delT	p.Val494fs	0.002	0	100	1	1,339
1 3	32,907,10 5	C	A	.	<i>BRCA2</i>	stop gained	c.1490C>A	p.Ser497*	0.005	0	100	1	1,339
1 3	32,907,28 0	AAATT	A	.	<i>BRCA2</i>	frameshift variant	c.1670_1674delTAATT	p.Leu557fs	0.002	0	99.99 9	1	354
1 3	32,907,37 5	CAAAT	C	rs80359303	<i>BRCA2</i>	frameshift variant	c.1763_1766delATAA	p.Asn588fs	0.002	0	100	1	573
1 3	32,907,38 2	GT	G	.	<i>BRCA2</i>	frameshift variant	c.1770delT	p.Phe590fs	0.002	0	100	1	573
1 3	32,907,42 0	GA	G	rs80359307	<i>BRCA2</i>	frameshift variant	c.1813delA	p.Ile605fs	0.071	0.008	100	1	573
1 3	32,907,42 0	G	GA	rs125340166 7; rs80359306	<i>BRCA2</i>	frameshift variant	c.1813dupA	p.Ile605fs	0.005	0	100	1	573
1 3	32,907,44 0	C	T	rs80358472	<i>BRCA2</i>	stop gained	c.1825C>T	p.Gln609*	0.002	0	100	1	513
1 3	32,907,52 5	G	A	rs587781629	<i>BRCA2</i>	splice donor variant & intron variant	c.1909+1G>A		0.003	0	100	1	412
1 3	32,910,58 8	AG	A	.	<i>BRCA2</i>	frameshift variant	c.2097delG	p.Gln699fs	0.002	0	100	1	597

1 3	32,910,62 5	C	A	.	<i>BRCA2</i>	stop gained	c.2133C>A	p.Cys711*	0.002	0	100	1	241
1 3	32,910,67 2	C	CA	.	<i>BRCA2</i>	frameshift variant	c.2181dupA	p.Asp728fs	0.002	0	100	1	480
1 3	32,910,85 9	AG	A	.	<i>BRCA2</i>	frameshift variant	c.2368delG	p.Glu790fs	0.002	0	100	1	947
1 3	32,911,00 5	AATAC	A	.	<i>BRCA2</i>	frameshift variant	c.2516_2519delACAT	p.Tyr839fs	0.003	0	100	1	300
1 3	32,911,03 9	A	ACC	.	<i>BRCA2</i>	frameshift variant	c.2548_2549insCC	p.Gln850fs	0.002	0	100	1	300
1 3	32,911,07 3	C	T	.	<i>BRCA2</i>	stop gained	c.2581C>T	p.Gln861*	0.002	0	100	1	510
1 3	32,911,15 8	AT	A	.	<i>BRCA2</i>	frameshift variant	c.2670delT	p.Phe890fs	0.003	0	99.99 9	1	362
1 3	32,911,29 3	GT	G	.	<i>BRCA2</i>	frameshift variant	c.2802delT	p.Asp935fs	0	0.003	100	1	1,545
1 3	32,911,29 7	TAAAC	T	rs80359351	<i>BRCA2</i>	frameshift variant	c.2808_2811delACAA	p.Ala938fs	0.005	0	100	1	1,545
1 3	32,911,32 1	TA	T	rs397509342	<i>BRCA2</i>	frameshift variant	c.2835delA	p.Asp946fs	0.002	0	100	1	1,179
1 3	32,911,40 4	T	A	.	<i>BRCA2</i>	stop gained	c.2912T>A	p.Leu971*	0.002	0	100	1	1,183
1 3	32,911,55 5	AC	A	.	<i>BRCA2</i>	frameshift variant	c.3064delC	p.His1022fs	0.002	0	99.99 9	1	354
1 3	32,911,68 3	CAATT	C	rs80359375	<i>BRCA2</i>	frameshift variant	c.3195_3198delTAAT	p.Asn1066fs	0.002	0	100	1	230
1 3	32,911,69 3	TG	T	rs397507658	<i>BRCA2</i>	frameshift variant	c.3202delG	p.Val1068fs	0.002	0	100	1	230
1 3	32,911,72 4	GT	G	rs397507660	<i>BRCA2</i>	frameshift variant	c.3235delT	p.Ser1079fs	0	0.003	100	1	454
1 3	32,911,78 8	C	G	rs397507663	<i>BRCA2</i>	stop gained	c.3296C>G	p.Ser1099*	0.002	0	100	1	933
1 3	32,911,96 9	CAG	C	.	<i>BRCA2</i>	frameshift variant	c.3481_3482delGA	p.Asp1161fs	0	0.003	100	1	709
1 3	32,912,00 0	G	GC	.	<i>BRCA2</i>	frameshift variant	c.3512dupC	p.Ser1172fs	0.002	0	100	1	1,328
1 3	32,912,06 2	GA	G	.	<i>BRCA2</i>	frameshift variant	c.3572delA	p.Lys1191fs	0.003	0	100	1	1,235

1 3	32,912,08 9	CTG	C	rs80359391	<i>BRCA2</i>	frameshift variant	c.3599_3600delGT	p.Cys1200fs	0.005	0.008	100	1	1,237
1 3	32,912,09 1	G	GTT	.	<i>BRCA2</i>	frameshift variant	c.3600_3601insTT	p.Asn1201fs	0.002	0	100	1	1,236
1 3	32,912,09 5	CA	C	.	<i>BRCA2</i>	frameshift variant	c.3607delA	p.Ser1203fs	0.002	0	100	1	1,236
1 3	32,912,14 0	TA	T	rs864622134	<i>BRCA2</i>	frameshift variant	c.3649delA	p.Arg1217fs	0.006	0	100	1	616
1 3	32,912,23 3	TAGTG	T	rs133892808 4; rs80359403	<i>BRCA2</i>	frameshift variant	c.3744_3747delTGAG	p.Ser1248fs	0.002	0	100	1	751
1 3	32,912,31 8	GA	G	rs397507689	<i>BRCA2</i>	frameshift variant	c.3830delA	p.Asn1277fs	0.002	0	100	1	804
1 3	32,912,32 8	AT	A	rs80359404	<i>BRCA2</i>	frameshift variant	c.3837delT	p.Asn1279fs	0.002	0	100	1	804
1 3	32,912,33 7	CTG	C	rs122926791 4; rs80359405	<i>BRCA2</i>	frameshift variant	c.3847_3848delGT	p.Val1283fs	0.002	0	100	1	855
1 3	32,912,38 7	G	T	.	<i>BRCA2</i>	stop gained	c.3895G>T	p.Glu1299*	0.002	0	100	1	855
1 3	32,912,43 2	A	T	.	<i>BRCA2</i>	stop gained	c.3940A>T	p.Lys1314*	0.005	0	99.83 7	1	165
1 3	32,912,51 1	AT	A	rs397507702	<i>BRCA2</i>	frameshift variant	c.4021delT	p.Ser1341fs	0.002	0	100	1	517
1 3	32,912,51 4	C	A	rs113540190 1	<i>BRCA2</i>	stop gained	c.4022C>A	p.Ser1341*	0.003	0	100	1	517
1 3	32,912,55 7	C	CT	.	<i>BRCA2</i>	frameshift variant	c.4067dupT	p.Leu1356fs	0.002	0	100	1	403
1 3	32,912,65 5	CTTTT	C	.	<i>BRCA2</i>	frameshift variant	c.4166_4169delTTTT	p.Phe1389fs	0.002	0	100	1	502
1 3	32,912,75 1	ATTTTG AGACTT CTGATA CAT	A	.	<i>BRCA2</i>	frameshift variant	c.4264_4283delGAGACTT CTGATACATTTT	p.Glu1422fs	0.002	0	100	1	2,214
1 3	32,912,77 0	A	AT	rs100580515 6; rs80359439	<i>BRCA2</i>	frameshift variant	c.4284dupT	p.Gln1429fs	0	0.003	100	1	2,116

1 3	32,912,77 6	T	TC	.	<i>BRCA2</i>	frameshift variant	c.4285dupC	p.Gln1429fs	0.002	0	100	1	2,116
1 3	32,912,83 0	TG	T	rs80359443	<i>BRCA2</i>	frameshift variant	c.4339delG	p.Val1447fs	0.006	0.003	100	1	1,131
1 3	32,912,95 2	AAC	A	rs106479717 6; rs397507720	<i>BRCA2</i>	frameshift variant	c.4464_4465delCA	p.His1488fs	0.002	0	100	1	1,484
1 3	32,912,96 1	TACTG	T	rs144295301 2; rs80359451	<i>BRCA2</i>	frameshift variant	c.4471_4474delCTGA	p.Leu1491fs	0.002	0	100	1	1,484
1 3	32,912,96 4	TGAAA	T	rs138044676 4; rs80359454	<i>BRCA2</i>	frameshift variant	c.4478_4481delAAAG	p.Glu1493fs	0	0.003	100	1	1,484
1 3	32,913,02 9	GATGA	G	.	<i>BRCA2</i>	frameshift variant	c.4539_4542delTGAA	p.Asp1513fs	0.003	0	100	1	1,902
1 3	32,913,13 8	AAG	A	.	<i>BRCA2</i>	frameshift variant	c.4649_4650delAG	p.Glu1550fs	0.005	0.003	100	1	2,318
1 3	32,913,21 1	T	TA	rs879255453	<i>BRCA2</i>	frameshift variant	c.4722dupA	p.Asp1575fs	0.002	0	100	1	1,994
1 3	32,913,26 1	AGT	A	.	<i>BRCA2</i>	frameshift variant	c.4772_4773delGT	p.Cys1591fs	0.002	0	99.99 9	1	834
1 3	32,913,29 5	T	TA	rs80359466	<i>BRCA2</i>	frameshift variant	c.4808dupA	p.Asn1603fs	0	0.003	99.99 9	1	834
1 3	32,913,31 4	G	T	.	<i>BRCA2</i>	stop gained	c.4822G>T	p.Glu1608*	0.005	0.003	99.99 9	1	1,669
1 3	32,913,35 9	C	T	.	<i>BRCA2</i>	stop gained	c.4867C>T	p.Gln1623*	0	0.003	100	1	1,741
1 3	32,913,39 1	CTT	C	.	<i>BRCA2</i>	frameshift variant	c.4903_4904delTT	p.Leu1635fs	0.005	0	100	1	1,741
1 3	32,913,43 5	CA	C	.	<i>BRCA2</i>	frameshift variant	c.4948delA	p.Ser1650fs	0.002	0	100	1	908
1 3	32,913,44 2	TC	T	rs397507752	<i>BRCA2</i>	frameshift variant	c.4952delC	p.Pro1651fs	0	0.005	100	1	908
1 3	32,913,45 7	C	A	rs80358721	<i>BRCA2</i>	stop gained	c.4965C>A	p.Tyr1655*	0.002	0	100	1	1,820
1 3	32,913,55 8	C	CA	rs126502817 4; rs80359480	<i>BRCA2</i>	frameshift variant	c.5073dupA	p.Trp1692fs	0.003	0.003	100	1	1,375

1 3	32,913,57 1	TAGAG	T	.	<i>BRCA2</i>	frameshift variant	c.5081_5084delGAGA	p.Arg1694fs	0.003	0	100	1	1,375
1 3	32,913,59 7	CAGAA	C	rs136279144 7; rs879254123	<i>BRCA2</i>	frameshift variant	c.5110_5113delAGAA	p.Arg1704fs	0.002	0	100	1	461
1 3	32,913,61 9	TTATG	T	rs120903225 9; rs80359484	<i>BRCA2</i>	frameshift variant	c.5130_5133delTGTA	p.Tyr1710fs	0.003	0	100	1	461
1 3	32,913,76 3	T	A	.	<i>BRCA2</i>	stop gained	c.5271T>A	p.Tyr1757*	0.002	0	100	1	1,509
1 3	32,913,77 1	C	A	.	<i>BRCA2</i>	stop gained	c.5279C>A	p.Ser1760*	0.002	0	100	1	1,509
1 3	32,913,84 4	C	CA	rs886040590	<i>BRCA2</i>	frameshift variant	c.5353dupA	p.Thr1785fs	0.002	0	100	1	2,097
1 3	32,913,90 0	CTG	C	rs80359512	<i>BRCA2</i>	frameshift variant	c.5410_5411delGT	p.Val1804fs	0.002	0	100	1	1,050
1 3	32,913,91 9	C	A	.	<i>BRCA2</i>	stop gained	c.5427C>A	p.Cys1809*	0.002	0	100	1	1,421
1 3	32,913,97 0	CATTAA	C	rs80359516	<i>BRCA2</i>	frameshift variant	c.5482_5486delAAATT	p.Lys1828fs	0.014	0.005	99.99 9	1	371
1 3	32,914,04 8	TTG	T	rs397507787	<i>BRCA2</i>	frameshift variant	c.5560_5561delGT	p.Val1854fs	0.003	0	99.99 9	1	371
1 3	32,914,06 5	CAATT	C	rs125515141 6; rs80359520	<i>BRCA2</i>	frameshift variant	c.5576_5579delTTAA	p.Ile1859fs	0.136	0.011	100	1	623
1 3	32,914,08 7	A	AT	.	<i>BRCA2</i>	frameshift variant	c.5598dupT	p.Thr1867fs	0.003	0	100	1	624
1 3	32,914,12 7	G	T	rs55996097	<i>BRCA2</i>	stop gained	c.5635G>T	p.Glu1879*	0	0.003	100	1	624
1 3	32,914,13 7	C	A	rs80358785	<i>BRCA2</i>	stop gained	c.5645C>A	p.Ser1882*	0.030	0.011	100	1	624
1 3	32,914,13 7	CA	C	.	<i>BRCA2</i>	frameshift variant	c.5650delA	p.Ile1884fs	0.002	0	100	1	624
1 3	32,914,16 5	AG	A	.	<i>BRCA2</i>	frameshift variant	c.5675delG	p.Gly1892fs	0.003	0	100	1	253
1 3	32,914,17 4	C	G	rs41293497	<i>BRCA2</i>	stop gained	c.5682C>G	p.Tyr1894*	0.005	0	100	1	506

1 3	32,914,19 9	AT	A	.	<i>BRCA2</i>	frameshift variant	c.5709delT	p.Leu1904fs	0.002	0	100	1	253
1 3	32,914,20 9	ACT	A	rs80359530	<i>BRCA2</i>	frameshift variant	c.5722_5723delCT	p.Leu1908fs	0.008	0.008	100	1	253
1 3	32,914,26 0	ACATT	A	rs80359535	<i>BRCA2</i>	frameshift variant	c.5771_5774delTTCA	p.Ile1924fs	0.003	0	100	1	660
1 3	32,914,26 4	TCA	T	.	<i>BRCA2</i>	frameshift variant	c.5773_5774delCA	p.Gln1925fs	0.003	0	100	1	660
1 3	32,914,47 2	C	T	rs80358831	<i>BRCA2</i>	stop gained	c.5980C>T	p.Gln1994*	0.002	0	100	1	1,057
1 3	32,914,50 3	AAGAT	A	rs105751863 5	<i>BRCA2</i>	frameshift variant	c.6014_6017delATAG	p.Asp2005fs	0.005	0	100	1	1,057
1 3	32,914,55 2	ACATT	A	.	<i>BRCA2</i>	frameshift variant	c.6063_6066delTTCA	p.His2021fs	0.005	0	100	1	1,310
1 3	32,914,57 7	G	T	rs397507828	<i>BRCA2</i>	stop gained	c.6085G>T	p.Glu2029*	0.002	0	100	1	1,118
1 3	32,914,73 4	AG	A	.	<i>BRCA2</i>	frameshift variant	c.6244delG	p.Glu2082fs	0.002	0	100	1	466
1 3	32,914,73 6	G	T	rs886040642	<i>BRCA2</i>	stop gained	c.6244G>T	p.Glu2082*	0.002	0	100	1	466
1 3	32,914,79 0	CA	C	rs397507839	<i>BRCA2</i>	frameshift variant	c.6302delA	p.Asn2101fs	0.002	0	100	1	1,024
1 3	32,914,81 7	GT	G	.	<i>BRCA2</i>	frameshift variant	c.6327delT	p.Asp2110fs	0.003	0	100	1	559
1 3	32,914,83 9	AC	A	.	<i>BRCA2</i>	frameshift variant	c.6348delC	p.Cys2117fs	0.005	0	100	1	558
1 3	32,914,85 1	C	A	.	<i>BRCA2</i>	stop gained	c.6359C>A	p.Ser2120*	0.002	0	100	1	558
1 3	32,914,85 9	G	GA	rs80359577	<i>BRCA2</i>	frameshift variant	c.6373dupA	p.Thr2125fs	0.002	0	100	1	558
1 3	32,914,89 3	ATAACT	A	rs80359584	<i>BRCA2</i>	frameshift variant	c.6405_6409delCTTAA	p.Asn2135fs	0.028	0.013	100	1	559
1 3	32,914,89 7	CTTAAA TG	C	rs397507851	<i>BRCA2</i>	frameshift variant	c.6408_6414delAAATGTT	p.Asn2137fs	0.002	0	100	1	559
1 3	32,914,90 6	TG	T	.	<i>BRCA2</i>	frameshift variant	c.6415delG	p.Glu2139fs	0.002	0	100	1	1,119
1 3	32,914,93 5	CTA	C	rs80359592	<i>BRCA2</i>	frameshift variant	c.6445_6446delAT	p.Ile2149fs	0.003	0	100	1	610

1 3	32,914,93 6	TATCAA	T	rs80359593	<i>BRCA2</i>	frameshift variant	c.6446_6450delTTAAA	p.Ile2149fs	0.003	0	100	1	610
1 3	32,914,95 1	ATATCT CTCTCA AT	A	.	<i>BRCA2</i>	frameshift variant	c.6461_6473delATCTCTC TCAATT	p.Tyr2154fs	0.002	0	100	1	609
1 3	32,914,95 3	ATC	A	rs80359596	<i>BRCA2</i>	frameshift variant	c.6468_6469delTC	p.Gln2157fs	0.006	0	100	1	609
1 3	32,914,95 4	T	G	rs80358883	<i>BRCA2</i>	stop gained	c.6462T>G	p.Tyr2154*	0.005	0	100	1	609
1 3	32,914,96 3	AT	A	.	<i>BRCA2</i>	frameshift variant	c.6474delT	p.Gln2159fs	0.002	0	100	1	609
1 3	32,914,97 3	GACAA	G	rs123213957 7; rs80359598	<i>BRCA2</i>	frameshift variant	c.6486_6489delACAA	p.Lys2162fs	0.002	0	100	1	610
1 3	32,915,00 7	CA	C	.	<i>BRCA2</i>	frameshift variant	c.6516delA	p.Val2174fs	0.002	0	100	1	996
1 3	32,915,04 3	AG	A	rs80359603	<i>BRCA2</i>	frameshift variant	c.6553delG	p.Ala2185fs	0.005	0.003	100	1	876
1 3	32,915,11 4	AAT	A	rs80359610	<i>BRCA2</i>	frameshift variant	c.6626_6627delTA	p.Ile2209fs	0.002	0	100	1	598
1 3	32,915,14 1	A	T	.	<i>BRCA2</i>	stop gained	c.6649A>T	p.Lys2217*	0.005	0	100	1	598
1 3	32,915,14 8	C	A	.	<i>BRCA2</i>	stop gained	c.6656C>A	p.Ser2219*	0.003	0	100	1	598
1 3	32,915,14 8	C	G	rs80358893	<i>BRCA2</i>	stop gained	c.6656C>G	p.Ser2219*	0.002	0	100	1	598
1 3	32,915,18 8	AG	A	.	<i>BRCA2</i>	frameshift variant	c.6697delG	p.Ala2233fs	0.002	0	99.95 7	1	158
1 3	32,915,21 2	GAC	G	.	<i>BRCA2</i>	frameshift variant	c.6722_6723delCA	p.Thr2241fs	0.002	0	99.96	1	158
1 3	32,915,29 2	C	G	.	<i>BRCA2</i>	stop gained	c.6800C>G	p.Ser2267*	0.002	0	99.96 1	1	161
1 3	32,918,77 5	A	T	.	<i>BRCA2</i>	stop gained	c.6922A>T	p.Lys2308*	0.008	0.003	99.15 2	1	240
1 3	32,918,77 8	AG	A	.	<i>BRCA2</i>	frameshift variant	c.6926delG	p.Ser2309fs	0.002	0	99.15 4	1	240

1 3	32,920,96 2	A	G	rs81002863	<i>BRCA2</i>	splice acceptor variant & intron variant	c.6938-2A>G		0.002	0	100	1	8,822
1 3	32,920,97 8	C	T	rs80358920	<i>BRCA2</i>	stop gained	c.6952C>T	p.Arg2318*	0.169	0.027	100	1	8,822
1 3	32,929,05 0	C	T	rs80358936	<i>BRCA2</i>	stop gained	c.7060C>T	p.Gln2354*	0.002	0	100	1	2,131
1 3	32,929,14 3	G	GT	rs80359639	<i>BRCA2</i>	frameshift variant	c.7156dupT	p.Ser2386fs	0.002	0	100	1	1,557
1 3	32,929,19 9	CAA	C	rs80359642	<i>BRCA2</i>	frameshift variant	c.7211_7212delAA	p.Lys2404fs	0.002	0	100	1	507
1 3	32,929,29 9	AT	A	.	<i>BRCA2</i>	frameshift variant	c.7311delT	p.Ile2437fs	0.002	0	100	1	1,165
1 3	32,929,42 0	C	CT	rs779007406; rs886038168	<i>BRCA2</i>	frameshift variant & splice region variant	c.7433dupT	p.Leu2478fs	0.002	0	100	1	688
1 3	32,930,56 3	A	T	rs397507917	<i>BRCA2</i>	splice acceptor variant & intron variant	c.7436-2A>T		0.002	0	100	1	998
1 3	32,930,56 4	G	T	.	<i>BRCA2</i>	splice acceptor variant & intron variant	c.7436-1G>T		0.002	0	100	1	998
1 3	32,930,60 9	C	T	rs80358972	<i>BRCA2</i>	stop gained	c.7480C>T	p.Arg2494*	0	0.003	100	1	1,994
1 3	32,930,68 7	C	T	rs80358981	<i>BRCA2</i>	stop gained	c.7558C>T	p.Arg2520*	0.009	0	100	1	1,578
1 3	32,930,71 3	AG	A	.	<i>BRCA2</i>	frameshift variant	c.7586delG	p.Gly2529fs	0.002	0	100	1	2,158
1 3	32,930,74 4	C	T	rs886040720	<i>BRCA2</i>	stop gained & splice region variant	c.7615C>T	p.Gln2539*	0.002	0	100	1	1,164
1 3	32,931,93 1	CAG	C	rs80359672	<i>BRCA2</i>	frameshift variant	c.7673_7674delAG	p.Glu2558fs	0.002	0	100	1	807
1 3	32,931,96 3	T	TG	.	<i>BRCA2</i>	frameshift variant	c.7702_7703insG	p.Phe2568fs	0.002	0	100	1	798
1 3	32,931,97 6	GTT	G	.	<i>BRCA2</i>	frameshift variant	c.7717_7718delTT	p.Leu2573fs	0.002	0	100	1	798

1 3	32,931,99 9	C	T	rs80358999	<i>BRCA2</i>	stop gained	c.7738C>T	p.Gln2580*	0.002	0	100	1	1,278
1 3	32,932,00 2	T	TTGGC TGA	.	<i>BRCA2</i>	frameshift variant & stop gained	c.7745_7751dupCTGATG G	p.Gly2585fs	0.002	0	100	1	962
1 3	32,932,05 3	G	T	rs113540191 9	<i>BRCA2</i>	stop gained	c.7792G>T	p.Glu2598*	0.002	0	100	1	481
1 3	32,936,65 9	G	T	rs81002860	<i>BRCA2</i>	splice acceptor variant & intron variant	c.7806-1G>T		0.003	0	99.99 9	1	281
1 3	32,936,73 0	TG	T	.	<i>BRCA2</i>	frameshift variant	c.7878delG	p.Trp2626fs	0.002	0	99.99 9	1	282
1 3	32,936,73 2	G	A	rs80359013	<i>BRCA2</i>	stop gained	c.7878G>A	p.Trp2626*	0.002	0	99.99 9	1	282
1 3	32,936,80 5	A	AG	.	<i>BRCA2</i>	frameshift variant	c.7954dupG	p.Val2652fs	0.002	0	99.99 9	1	281
1 3	32,936,82 3	A	T	.	<i>BRCA2</i>	stop gained	c.7969A>T	p.Lys2657*	0.003	0	99.99 9	1	281
1 3	32,936,83 1	G	T	.	<i>BRCA2</i>	splice donor variant & intron variant	c.7976+1G>T		0.002	0	99.99 9	1	281
1 3	32,937,36 2	A	G	rs397507954	<i>BRCA2</i>	missense variant	c.8023A>G	p.Ile2675Val	0.025	0.005	100	1	833
1 3	32,937,37 7	GAC	G	rs276174901	<i>BRCA2</i>	frameshift variant	c.8042_8043delCA	p.Thr2681fs	0.002	0	100	1	835
1 3	32,937,47 9	C	T	rs80359058	<i>BRCA2</i>	stop gained	c.8140C>T	p.Gln2714*	0	0.003	100	1	1,344
1 3	32,937,50 7	A	G	rs41293513	<i>BRCA2</i>	missense variant	c.8168A>G	p.Asp2723Gl y	0.005	0	100	1	1,344
1 3	32,937,58 2	G	A	rs80359071	<i>BRCA2</i>	missense variant	c.8243G>A	p.Gly2748As p	0.005	0	100	1	511
1 3	32,944,57 1	G	A	rs397507981	<i>BRCA2</i>	stop gained	c.8364G>A	p.Trp2788*	0.002	0	99.97 8	1	584
1 3	32,944,69 6	T	C	rs886040944	<i>BRCA2</i>	splice donor variant & intron variant	c.8487+2T>C		0.002	0	99.97 6	1	584
1 3	32,945,17 2	AG	A	.	<i>BRCA2</i>	frameshift variant	c.8569delG	p.Ala2857fs	0.002	0	98.79 6	1	69

1 3	32,950,82 5	ATT	A	.	<i>BRCA2</i>	frameshift variant	c.8653_8654delTT	p.Leu2885fs	0.003	0	100	1	1,132
1 3	32,950,93 0	T	A	.	<i>BRCA2</i>	splice donor variant & intron variant	c.8754+2T>A		0.002	0	100	1	566
1 3	32,953,54 4	AGGAA GGCCA T	A	.	<i>BRCA2</i>	frameshift variant	c.8850_8859delGGCCAT GGAA	p.Lys2950fs	0.002	0	100	1	1,868
1 3	32,953,63 2	C	G	rs80359144	<i>BRCA2</i>	stop gained	c.8933C>G	p.Ser2978*	0.002	0	100	1	630
1 3	32,953,65 3	G	T	rs81002882	<i>BRCA2</i>	splice donor variant & intron variant	c.8953+1G>T		0.002	0	100	1	652
1 3	32,953,88 5	A	G	.	<i>BRCA2</i>	splice acceptor variant & intron variant	c.8954-2A>G		0.002	0	99.99 9	1	226
1 3	32,953,89 7	TA	T	rs886040807	<i>BRCA2</i>	frameshift variant	c.8965delA	p.Ile2989fs	0.002	0	99.99 9	1	226
1 3	32,953,98 5	AG	A	.	<i>BRCA2</i>	frameshift variant	c.9053delG	p.Ser3018fs	0.002	0	99.99 9	1	456
1 3	32,954,00 9	C	T	rs80359159	<i>BRCA2</i>	stop gained	c.9076C>T	p.Gln3026*	0.039	0.008	99.99 9	1	230
1 3	32,954,02 2	C	CA	rs130565336 1	<i>BRCA2</i>	frameshift variant	c.9097dupA	p.Thr3033fs	0.008	0	99.99 9	1	230
1 3	32,954,04 2	C	T	rs397508037	<i>BRCA2</i>	stop gained	c.9109C>T	p.Gln3037*	0.005	0	99.99 9	1	231
1 3	32,954,05 0	G	A	rs28897756	<i>BRCA2</i>	splice region variant & synonymous variant	c.9117G>A	p.Pro3039Pr o	0.016	0.003	99.99 9	1	231
1 3	32,954,27 2	G	GA	rs80359752; rs886038189	<i>BRCA2</i>	frameshift variant & splice region variant	c.9253dupA	p.Thr3085fs	0.002	0	99.99 8	1	371
1 3	32,968,95 1	C	T	rs80359212	<i>BRCA2</i>	stop gained	c.9382C>T	p.Arg3128*	0.009	0.003	100	1	1,463
1 3	32,971,15 3	T	TC	.	<i>BRCA2</i>	frameshift variant	c.9621dupC	p.Ile3208fs	0.002	0	100	1	358

1 3	32,971,18 2	G	T	.	<i>BRCA2</i>	splice donor variant & intron variant	c.9648+1G>T		0.002	0.003	100	1	358
1 7	41,197,72 9	T	C	rs80357258	<i>BRCA1</i>	missense variant	c.5621A>G	p.Tyr1874Cys	0.011	0	100	1	1,159
1 7	41,197,76 6	T	TG	.	<i>BRCA1</i>	frameshift variant	c.5583dupC	p.Ser1862fs	0.002	0	100	1	2,317
1 7	41,197,78 4	G	A	rs41293465	<i>BRCA1</i>	stop gained	c.5566C>T	p.Arg1856*	0.003	0	100	1	2,318
1 7	41,199,65 9	C	T	rs80358145	<i>BRCA1</i>	splice donor variant & intron variant	c.5530+1G>A		0.003	0	100	1	1,564
1 7	41,201,18 3	AC	A	.	<i>BRCA1</i>	frameshift variant	c.5423delG	p.Cys1808fs	0.002	0	100	1	2,640
1 7	41,203,13 5	C	G	rs80358099	<i>BRCA1</i>	splice acceptor variant & intron variant	c.5341-1G>C		0.002	0.003	100	1	810
1 7	41,209,09 5	G	A	rs80357123	<i>BRCA1</i>	stop gained	c.5314C>T	p.Arg1772*	0.003	0	100	1	2,097
1 7	41,209,13 1	CT	C	.	<i>BRCA1</i>	frameshift variant	c.5277delA	p.Asp1760fs	0.002	0	100	1	2,095
1 7	41,209,13 3	CCT	C	.	<i>BRCA1</i>	frameshift variant	c.5274_5275delAG	p.Gly1759fs	0.002	0	100	1	1,075
1 7	41,209,13 4	C	T	rs80356937	<i>BRCA1</i>	missense variant	c.5275G>A	p.Gly1759Arg	0.002	0	100	1	1,049
1 7	41,215,34 9	C	T	rs80358004	<i>BRCA1</i>	splice donor variant & intron variant	c.5256+1G>A		0.003	0	100	1	810
1 7	41,215,38 2	G	A	rs878854957	<i>BRCA1</i>	stop gained	c.5224C>T	p.Gln1742*	0.005	0.003	100	1	811
1 7	41,215,89 5	A	T	rs397509230	<i>BRCA1</i>	stop gained	c.5211T>A	p.Tyr1737*	0.002	0	100	1	615
1 7	41,215,92 0	G	T	rs28897696	<i>BRCA1</i>	missense variant	c.5186C>A	p.Ala1729Gl	0.002	0	100	1	615

1 7	41,215,94 7	C	T	rs41293459	<i>BRCA1</i>	missense variant	c.5159G>A	p.Arg1720Gln	0.011	0.008	100	1	1,230
1 7	41,215,94 8	G	A	rs55770810	<i>BRCA1</i>	missense variant	c.5158C>T	p.Arg1720Trp	0.002	0	100	1	1,230
1 7	41,215,95 1	C	A	.	<i>BRCA1</i>	stop gained	c.5155G>T	p.Glu1719*	0.002	0	100	1	1,229
1 7	41,215,95 4	A	G	rs80356993	<i>BRCA1</i>	missense variant	c.5152T>C	p.Cys1718Arg	0.002	0	100	1	1,230
1 7	41,215,96 9	C	G	rs1800747	<i>BRCA1</i>	splice acceptor variant & intron variant	c.5138-1G>C		0.002	0	100	1	1,230
1 7	41,219,62 5	C	G	rs80187739	<i>BRCA1</i>	missense variant & splice region variant	c.5137G>C	p.Asp1713His	0.002	0	100	1	1,587
1 7	41,219,63 4	TAAC	T	rs80358344	<i>BRCA1</i>	conservative inframe deletion	c.5125_5127delGTT	p.Val1709del	0.002	0	100	1	1,587
1 7	41,219,66 3	AG	A	rs80357896	<i>BRCA1</i>	frameshift variant	c.5098delC	p.Leu1700fs	0.002	0	100	1	1,586
1 7	41,219,66 5	ATTAG	A	rs80357580	<i>BRCA1</i>	frameshift variant	c.5093_5096delCTAA	p.Thr1698fs	0	0.003	100	1	1,586
1 7	41,223,03 1	T	TG	.	<i>BRCA1</i>	frameshift variant	c.4962dupC	p.Arg1655fs	0.002	0	100	1	653
1 7	41,223,05 4	T	TTATA	.	<i>BRCA1</i>	frameshift variant & stop gained	c.4936_4939dupTATA	p.Asn1647fs	0.002	0	100	1	826
1 7	41,223,06 0	C	CT	.	<i>BRCA1</i>	frameshift variant	c.4933_4934insA	p.Gly1645fs	0.002	0	100	1	826
1 7	41,226,41 1	G	A	rs80356992	<i>BRCA1</i>	stop gained	c.4675C>T	p.Gln1559*	0.003	0	100	1	1,202
1 7	41,226,54 0	T	C	rs80358054	<i>BRCA1</i>	splice acceptor variant & intron variant	c.4548-2A>G		0.005	0	100	1	1,202

1 7	41,228,51 5	CTGGT	C	.	<i>BRCA1</i>	frameshift variant	c.4533_4536delACCA	p.Pro1512fs	0.002	0	100	1	616
1 7	41,228,55 7	C	CA	.	<i>BRCA1</i>	frameshift variant	c.4494dupT	p.Glu1499fs	0.002	0	100	1	1,233
1 7	41,234,43 9	G	GTTCT	rs397509164	<i>BRCA1</i>	frameshift variant	c.4335_4338dupAGAA	p.Gln1447fs	0.013	0.003	99.99 9	1	321
1 7	41,234,45 1	G	A	rs41293455	<i>BRCA1</i>	stop gained	c.4327C>T	p.Arg1443*	0.003	0	99.99 9	1	321
1 7	41,234,52 3	C	A	rs80357309	<i>BRCA1</i>	stop gained	c.4255G>T	p.Glu1419*	0.002	0	99.99 9	1	321
1 7	41,234,57 7	G	A	rs397509151	<i>BRCA1</i>	stop gained	c.4201C>T	p.Gln1401*	0.002	0	99.99 9	1	321
1 7	41,242,96 0	C	T	rs80358076	<i>BRCA1</i>	splice donor variant & intron variant	c.4185+1G>A		0.002	0	100	1	1,023
1 7	41,242,96 1	C	T	rs80356857	<i>BRCA1</i>	splice region variant & synonymous variant	c.4185G>A	p.Gln1395Gl n	0.003	0	100	1	1,023
1 7	41,242,97 9	ACT	A	rs80357572	<i>BRCA1</i>	frameshift variant	c.4165_4166delAG	p.Ser1389fs	0.003	0	100	1	1,023
1 7	41,242,98 3	TGA	T	rs80357565	<i>BRCA1</i>	frameshift variant	c.4161_4162delTC	p.Gln1388fs	0.002	0	100	1	1,023
1 7	41,243,00 8	CAG	C	rs397509141	<i>BRCA1</i>	frameshift variant	c.4136_4137delCT	p.Ser1379fs	0.002	0	100	1	1,023
1 7	41,243,02 4	ACT	A	rs80357787	<i>BRCA1</i>	frameshift variant	c.4120_4121delAG	p.Ser1374fs	0.006	0	100	1	1,024
1 7	41,243,47 0	TTTGCT CTTCTT GATTAT TTTCTT CC	T	.	<i>BRCA1</i>	frameshift variant	c.4053_4077delGGAAGA AAATAATCAAGAAGAGCA A	p.Glu1352fs	0.002	0	100	1	982
1 7	41,243,50 5	CCT	C	rs80357727	<i>BRCA1</i>	frameshift variant	c.4041_4042delAG	p.Gly1348fs	0.002	0	100	1	982

1 7	41,243,53 9	C	CA	.	<i>BRCA1</i>	frameshift variant	c.4008dupT	p.Asp1337fs	0.002	0	100	1	983
1 7	41,243,56 9	G	A	rs876659720	<i>BRCA1</i>	stop gained	c.3979C>T	p.Gln1327*	0.002	0	100	1	2,850
1 7	41,243,61 5	GT	G	rs80357504	<i>BRCA1</i>	frameshift variant	c.3932delA	p.Asn1311fs	0.002	0	100	1	1,866
1 7	41,243,65 8	GA	G	rs886038027	<i>BRCA1</i>	frameshift variant	c.3889delT	p.Ser1297fs	0.002	0	100	1	1,868
1 7	41,243,70 7	G	A	rs80356866	<i>BRCA1</i>	stop gained	c.3841C>T	p.Gln1281*	0.002	0	100	1	921
1 7	41,243,77 6	CCT	C	rs136953439 4; rs80357579	<i>BRCA1</i>	frameshift variant	c.3770_3771delAG	p.Glu1257fs	0.002	0	100	1	920
1 7	41,243,88 2	CT	C	.	<i>BRCA1</i>	frameshift variant	c.3665delA	p.Glu1222fs	0.002	0	100	1	966
1 7	41,243,90 1	A	C	rs397509091	<i>BRCA1</i>	stop gained	c.3647T>G	p.Leu1216*	0.003	0	100	1	966
1 7	41,243,90 8	C	A	rs80356923	<i>BRCA1</i>	stop gained	c.3640G>T	p.Glu1214*	0.008	0	100	1	965
1 7	41,243,94 1	G	A	rs62625308	<i>BRCA1</i>	stop gained	c.3607C>T	p.Arg1203*	0.002	0	100	1	488
1 7	41,243,96 7	G	GTGAA	.	<i>BRCA1</i>	frameshift variant	c.3577_3580dupTTCA	p.Thr1194fs	0.002	0	100	1	798
1 7	41,244,00 4	G	A	rs80357296	<i>BRCA1</i>	stop gained	c.3544C>T	p.Gln1182*	0.003	0.003	99.99 7	1	312
1 7	41,244,03 8	AATGTC	A	rs397509078	<i>BRCA1</i>	frameshift variant	c.3505_3509delGACAT	p.Asp1169fs	0.002	0	99.99 8	1	312
1 7	41,244,08 5	C	CT	rs80357857	<i>BRCA1</i>	frameshift variant	c.3462dupA	p.Asp1155fs	0.002	0	99.99 7	1	303
1 7	41,244,10 5	TC	T	rs80357808	<i>BRCA1</i>	frameshift variant	c.3442delG	p.Glu1148fs	0.011	0	99.99 6	1	302
1 7	41,244,14 5	G	A	rs80357136	<i>BRCA1</i>	stop gained	c.3403C>T	p.Gln1135*	0.002	0	100	1	1,506
1 7	41,244,14 9	TAA	T	rs80357577	<i>BRCA1</i>	frameshift variant	c.3397_3398delTT	p.Leu1133fs	0.003	0	100	1	1,506
1 7	41,244,15 9	GA	G	rs886040123	<i>BRCA1</i>	frameshift variant	c.3388delT	p.Ser1130fs	0.002	0	100	1	1,506

1 7	41,244,21 8	CT	C	rs397509056	<i>BRCA1</i>	frameshift variant	c.3329delA	p.Lys1110fs	0.002	0	100	1	2,428
1 7	41,244,25 0	C	A	.	<i>BRCA1</i>	stop gained	c.3298G>T	p.Gly1100*	0.002	0	100	1	1,221
1 7	41,244,25 8	CTT	C	rs80357686	<i>BRCA1</i>	frameshift variant	c.3288_3289delAA	p.Leu1098fs	0.002	0	100	1	1,221
1 7	41,244,29 1	A	C	rs80357006	<i>BRCA1</i>	stop gained	c.3257T>G	p.Leu1086*	0.005	0	100	1	2,070
1 7	41,244,31 8	CCT	C	rs80357635	<i>BRCA1</i>	frameshift variant	c.3228_3229delAG	p.Gly1077fs	0.002	0	100	1	850
1 7	41,244,42 6	G	C	rs397509035	<i>BRCA1</i>	stop gained	c.3122C>G	p.Ser1041*	0.002	0	100	1	1,512
1 7	41,244,44 6	ATT	A	.	<i>BRCA1</i>	frameshift variant	c.3100_3101delAA	p.Asn1034fs	0.002	0	100	1	1,512
1 7	41,244,68 3	TGATAG	T	.	<i>BRCA1</i>	frameshift variant	c.2860_2864delCTATC	p.Leu954fs	0.002	0.003	100	1	470
1 7	41,244,68 7	AG	A	.	<i>BRCA1</i>	frameshift variant	c.2860delC	p.Leu954fs	0.002	0	100	1	470
1 7	41,244,74 8	G	A	rs80357223	<i>BRCA1</i>	stop gained	c.2800C>T	p.Gln934*	0.036	0	100	1	471
1 7	41,244,77 7	TTAAC	T	rs80357661	<i>BRCA1</i>	frameshift variant	c.2767_2770delGTAA	p.Val923fs	0.003	0	100	1	1,730
1 7	41,244,79 6	TGAT	GA	.	<i>BRCA1</i>	frameshift variant & missense variant	c.2749_2752delATCAinsTC	p.Ile917fs	0.002	0	100	1	1,729
1 7	41,244,86 9	C	CT	rs886040060	<i>BRCA1</i>	frameshift variant	c.2678dupA	p.Lys894fs	0.002	0	100	1	1,730
1 7	41,244,93 5	CGG	C	rs80357962	<i>BRCA1</i>	frameshift variant	c.2611_2612delCC	p.Pro871fs	0.002	0	100	1	1,250
1 7	41,244,99 7	C	A	rs398122662	<i>BRCA1</i>	stop gained	c.2551G>T	p.Glu851*	0.002	0	100	1	2,284
1 7	41,245,03 4	GT	G	rs80357863	<i>BRCA1</i>	frameshift variant	c.2513delA	p.Asn838fs	0.003	0	100	1	1,034
1 7	41,245,15 7	TTC	T	rs80357695	<i>BRCA1</i>	frameshift variant	c.2389_2390delGA	p.Glu797fs	0.022	0.005	100	1	1,406
1 7	41,245,24 7	GC	G	.	<i>BRCA1</i>	frameshift variant	c.2300delG	p.Ser767fs	0.002	0	100	1	749

1 7	41,245,27 8	AC	A	rs80357583	<i>BRCA1</i>	frameshift variant	c.2269delG	p.Val757fs	0.003	0	100	1	363
1 7	41,245,33 0	C	CT	rs80357802	<i>BRCA1</i>	frameshift variant	c.2217dupA	p.Val740fs	0.002	0	100	1	1,367
1 7	41,245,35 1	CTTCTT	C	rs397508946	<i>BRCA1</i>	frameshift variant	c.2192_2196delAAGAA	p.Lys731fs	0.002	0	100	1	1,367
1 7	41,245,39 0	C	A	rs80356875	<i>BRCA1</i>	stop gained	c.2158G>T	p.Glu720*	0.002	0	100	1	2,022
1 7	41,245,41 0	G	C	rs80357233	<i>BRCA1</i>	stop gained	c.2138C>G	p.Ser713*	0.002	0	100	1	2,023
1 7	41,245,43 3	TG	T	.	<i>BRCA1</i>	frameshift variant	c.2114delC	p.Ala705fs	0.002	0	100	1	2,023
1 7	41,245,44 5	CT	C	.	<i>BRCA1</i>	frameshift variant	c.2102delA	p.Lys701fs	0.002	0	100	1	2,023
1 7	41,245,47 1	CAT	C	rs397508936	<i>BRCA1</i>	frameshift variant	c.2075_2076delAT	p.His692fs	0.002	0	100	1	1,673
1 7	41,245,47 5	TC	T	.	<i>BRCA1</i>	frameshift variant	c.2072delG	p.Arg691fs	0.002	0	100	1	1,673
1 7	41,245,51 8	CCA	C	rs397508931	<i>BRCA1</i>	frameshift variant	c.2028_2029delTG	p.Gly677fs	0.002	0	100	1	655
1 7	41,245,58 6	C	CT	rs80357853	<i>BRCA1</i>	frameshift variant	c.1961dupA	p.Tyr655fs	0.002	0	100	1	1,338
1 7	41,245,58 6	CT	C	rs80357522	<i>BRCA1</i>	frameshift variant	c.1961delA	p.Lys654fs	0.002	0	100	1	1,338
1 7	41,245,59 4	T	TC	rs80357753	<i>BRCA1</i>	frameshift variant	c.1953dupG	p.Lys652fs	0.002	0	100	1	685
1 7	41,245,71 6	AG	A	rs397508913	<i>BRCA1</i>	frameshift variant	c.1831delC	p.Leu611fs	0.002	0	99.98 6	1	221
1 7	41,245,73 5	CT	C	rs80357927	<i>BRCA1</i>	frameshift variant	c.1812delA	p.Ala605fs	0.002	0	100	1	441
1 7	41,246,02 9	TC	T	rs80357947	<i>BRCA1</i>	frameshift variant	c.1518delG	p.Arg507fs	0.003	0	99.99 9	1	556
1 7	41,246,02 9	T	A	rs397508880	<i>BRCA1</i>	stop gained	c.1519A>T	p.Arg507*	0.002	0	99.99 9	1	556
1 7	41,246,03 9	CTTTAA	C	rs80357888	<i>BRCA1</i>	frameshift variant	c.1504_1508delTTAAA	p.Leu502fs	0.002	0	99.99 9	1	556
1 7	41,246,06 8	G	A	rs80357010	<i>BRCA1</i>	stop gained	c.1480C>T	p.Gln494*	0.002	0	99.99 9	1	556

1 7	41,246,10 1	TA	T	.	<i>BRCA1</i>	frameshift variant	c.1446delT	p.Ile483fs	0.002	0	99.99 9	1	557
1 7	41,246,16 9	AT	A	.	<i>BRCA1</i>	frameshift variant	c.1378delA	p.Ile460fs	0.002	0	99.99 9	1	556
1 7	41,246,25 5	TAAGTC TATTTC CTCTG	T	.	<i>BRCA1</i>	frameshift variant	c.1277_1292delCAGAGA AAATAGACTT	p.Ser426fs	0.005	0	100	1	830
1 7	41,246,42 7	GT	G	.	<i>BRCA1</i>	frameshift variant	c.1120delA	p.Thr374fs	0.002	0	100	1	1,259
1 7	41,246,43 5	AG	A	rs397508837	<i>BRCA1</i>	frameshift variant	c.1112delC	p.Pro371fs	0.002	0	100	1	1,260
1 7	41,246,63 7	A	AATTC	.	<i>BRCA1</i>	frameshift variant & stop gained	c.907_910dupGAAT	p.Phe304fs	0.003	0	100	1	2,317
1 7	41,246,74 2	A	T	.	<i>BRCA1</i>	stop gained	c.806T>A	p.Leu269*	0.002	0	99.99 9	1	359
1 7	41,247,91 7	G	A	rs397509301	<i>BRCA1</i>	stop gained	c.616C>T	p.Gln206*	0.003	0.003	100	1	2,164
1 7	41,251,83 4	G	A	rs80357133	<i>BRCA1</i>	stop gained	c.505C>T	p.Gln169*	0.003	0	100	1	782
1 7	41,251,88 1	CTG	C	rs80357882	<i>BRCA1</i>	frameshift variant	c.456_457delCA	p.Ser153fs	0.006	0.003	100	1	781
1 7	41,256,19 0	G	T	rs80356888	<i>BRCA1</i>	stop gained	c.390C>A	p.Tyr130*	0.003	0	100	1	469
1 7	41,256,23 6	GGA	G	rs80357881	<i>BRCA1</i>	frameshift variant	c.342_343delTC	p.Pro115fs	0.002	0	100	1	940
1 7	41,256,25 8	CA	C	rs80357544	<i>BRCA1</i>	frameshift variant	c.321delT	p.Phe107fs	0.002	0	100	1	480
1 7	41,256,28 0	T	G	rs80358011	<i>BRCA1</i>	splice acceptor variant & intron variant	c.302-2A>C		0.002	0	100	1	469
1 7	41,258,47 1	A	G	rs80358026	<i>BRCA1</i>	splice donor variant & intron variant	c.212+2T>C		0.002	0	100	1	576
1 7	41,258,49 5	A	G	rs80357064	<i>BRCA1</i>	missense variant	c.190T>C	p.Cys64Arg	0.002	0	100	1	576
1 7	41,258,49 7	A	T	rs80357086	<i>BRCA1</i>	stop gained	c.188T>A	p.Leu63*	0.122	0.022	100	1	576

1 7	41,258,55 2	T	G	.	<i>BRCA1</i>	splice acceptor variant & intron variant	c.135-2A>C		0.003	0	100	1	1,153
1 7	41,267,74 1	A	C	rs80358131	<i>BRCA1</i>	splice donor variant & intron variant	c.134+2T>G		0.002	0	100	1	640
1 7	41,267,74 4	TGC	T	.	<i>BRCA1</i>	frameshift variant & splice region variant	c.131_132delGC	p.Cys44fs	0.003	0	100	1	640
1 7	41,267,79 7	C	T	rs80358018	<i>BRCA1</i>	splice acceptor variant & intron variant	c.81-1G>A		0.003	0	100	1	1,279
1 7	41,276,04 7	C	CT	rs149154489 9; rs80357783	<i>BRCA1</i>	frameshift variant	c.66dupA	p.Glu23fs	0.002	0	100	1	1,481

Chromosome position is based on hg19. The effect of genetic variants on the amino acid sequence using the SnpEff ver4.3t. Protein position was reported according to CCDS11456 for *BRCA1* and CCDS9344 for *BRCA2*.

eTable 2. Comparison of *BRCA1* and *BRCA2* pathogenic variant frequency for all* patients for each cancer type, versus controls.

	<i>BRCA1</i>			<i>BRCA2</i>		
	Carrier frequency (%)		P value	Carrier frequency (%)		P value
Cancer type	Case	Control		Case	Control	
Biliary tract	1.056	0.057	2.76×10^{-13}	1.056	0.175	1.58×10^{-6}
Breast (female)	1.271	0.040	3.40×10^{-17}	2.532	0.149	1.58×10^{-38}
Breast (male)	1.887	0.071	1.07×10^{-3}	18.868	0.199	8.04×10^{-31}
Cervical	0.263	0.040	5.23×10^{-3}	0.631	0.149	1.94×10^{-3}
Colorectal	0.159	0.057	4.96×10^{-4}	0.311	0.175	1.72×10^{-3}
Endometrial	0.261	0.040	1.31×10^{-3}	0.522	0.149	1.94×10^{-3}
Esophageal	0.323	0.057	3.59×10^{-5}	0.738	0.175	7.16×10^{-8}
Gastric	0.273	0.057	8.59×10^{-9}	0.894	0.175	5.29×10^{-25}
Liver	0.194	0.057	2.04×10^{-3}	0.443	0.175	8.72×10^{-4}
Lung	0.243	0.057	3.02×10^{-6}	0.567	0.175	1.83×10^{-8}
Lymphoma	0.354	0.057	8.82×10^{-6}	0.472	0.175	0.012
Ovarian	4.860	0.040	8.96×10^{-34}	3.422	0.149	9.46×10^{-38}
Pancreatic	0.697	0.057	2.43×10^{-9}	2.291	0.175	6.40×10^{-27}
Prostate	0.162	0.071	0.012	1.009	0.199	1.36×10^{-17}
Renal	0.132	0.057	0.402	0.527	0.175	0.031

*Patients with reported family history were included. See methods for more details.

A logistic regression analysis under a dominant model with age at diagnosis for cases and age at registration for controls as covariate was used. We eliminated samples without age diagnosis or registration from this calculation.

eTable 3. Results of two sensitivity analyses in breast cancer.

Methods	BRCA1			BRCA2		
	OR	95 % CI	P value	OR	95 % CI	P value
1. Logistic regression analysis adjusting for region	23.0	9.7 - 54.8	1.35×10^{-12}	10.0	6.3 - 15.8	1.78×10^{-21}
2. Burden test in patients with breast cancer only	15.2	6.6 - 34.9	1.38×10^{-10}	10.7	6.8 - 16.8	9.23×10^{-23}

We conducted two sensitivity analyses in breast cancer to investigate a potential bias from population stratification and the presence of more than one cancer type. Both results were comparable to estimates from the main analysis shown in Table 2

eTable 4. Mean age at diagnosis of each cancer type in patients with or without pathogenic variants in *BRCA1* and *BRCA2*.

Cancer type	<i>BRCA1</i>					<i>BRCA2</i>										
	Carrier		Non-carrier		Difference	P value	Carrier		Non-carrier		Difference	P value				
Biliary tract	72.9	±	9.4	68.7	±	9.5	4.2	0.22	-	-	-	-				
Breast (female)	50.7	±	12.5	56.4	±	12.1	-5.7	2.06×10^{-6}	50.7	±	11.5	56.4 ± 12.1	-5.7	2.48×10^{-13}		
Breast (male)	-		-	-	-	-	-	-	71.9	±	9.6	67.0	±	10.1	4.9	0.19
Esophageal	-		-	-	-	-	-	-	60.9	±	7.7	65.2	±	8.5	-4.3	0.04
Gastric	62.3	±	12.0	65.7	±	10.5	-3.5	0.14	64.5	±	9.7	65.7	±	10.5	-1.3	0.22
Ovarian	55.8	±	10.1	53.5	±	12.3	2.3	0.07	57.5	±	9.8	53.5	±	12.2	4.1	6.31×10^{-3}
Pancreatic	61.6	±	8.2	67.2	±	9.9	-5.7	0.12	67.4	±	12.5	67.2	±	9.9	0.2	0.94
Prostate	-		-	-	-	-	-	-	68.1	±	8.0	70.3	±	7.2	-2.2	5.79×10^{-3}

t-test was used for this comparison. We eliminated samples without age at diagnosis. P = 0.01 in *BRCA1* and P = 7.14×10^{-3} in *BRCA2* were set at the threshold of significance.

eTable 5. Comparisons of histological subtypes between carriers with pathogenic variants and non-carriers.

(A) Biliary tract cancer		<i>BRCA1</i>			<i>BRCA2</i>		
Histological type		Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value
Papillary adenocarcinoma		16.7	11.9	0.60	-	-	NA
Tubular adenocarcinoma		83.3	73.9		-	-	
Others		0.0	14.2		-	-	
(B) Female breast cancer		<i>BRCA1</i>			<i>BRCA2</i>		
Histological type		Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value
Invasive papillotubular carcinoma		29.7	40.1	1.19×10^{-6}	35.1	40.1	2.95×10^{-3}
Invasive solid-tubular carcinoma		30.7	12.6		18.1	12.7	
Invasive scirrhous carcinoma		25.7	27.2		33.7	27.0	
Others		13.9	20.1		13.2	20.2	
(C) Esophageal cancer		<i>BRCA1</i>			<i>BRCA2</i>		
Histological type		Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value
Squamous cell carcinoma		-	-	NA	80.0	91.6	0.26
Others		-	-		20.0	8.4	

(D) Gastric cancer								
Histological type	BRCA1			BRCA2				
	Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value		
	73.1	66.7	0.62	65.9	66.7	0.16		
	19.2	17.4		21.2	17.4			
	7.7	10.7		4.7	10.8			
	0.0	5.2		8.2	5.1			
(E) Ovarian cancer								
Histological type	BRCA1			BRCA2				
	Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value		
	63.5	28.8	6.60×10 ⁻⁹	73.3	28.9	1.75×10 ⁻⁸		
	1.6	21.8		6.7	21.4			
	17.5	18.4		6.7	18.8			
	1.6	16.3		2.2	16.1			
	15.9	14.7		11.1	14.9			
(F) Pancreatic cancer								
Histological type	BRCA1			BRCA2				
	Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value		
	40.0	61.2	0.63	84.6	60.4	0.20		
	20.0	12.5		7.7	12.7			
	40.0	26.3		7.7	26.9			
(G) Prostate cancer								
Histological type	BRCA1			BRCA2				
	Carrier (%)	Non-carrier (%)	P value	Carrier (%)	Non-carrier (%)	P value		
	-	-	NA	100.0	99.5	1.00		
	-	-		0.0	0.5			

P-value was calculated using the χ^2 test.

5. Supplementary references

1. Spurdle AB, Healey S, Devereau A, et al. ENIGMA--evidence-based network for the interpretation of germline mutant alleles: an international initiative to evaluate risk and clinical significance associated with sequence variation in BRCA1 and BRCA2 genes. *Hum. Mutat.* 2012;33(1):2-7.
2. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan (Ministry of Health, Labour and Welfare, National Cancer Registry).
3. Koyanagi YN, Ito H, Oze I, et al. Development of a prediction model and estimation of cumulative risk for upper aerodigestive tract cancer on the basis of the aldehyde dehydrogenase 2 genotype and alcohol consumption in a Japanese population. *Eur. J. Cancer Prev.* 2017;26(1):38-47.
4. Crispo A, Brennan P, Jockel KH, et al. The cumulative risk of lung cancer among current, ex- and never-smokers in European men. *Br. J. Cancer.* 2004;91(7):1280-1286.
5. Peto R, Darby S, Deo H, Silcocks P, Whitley E, Doll R. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. *BMJ.* 2000;321(7257):323-329.
6. Giordano SH. Breast Cancer in Men. *N. Engl. J. Med.* 2018;378(24):2311-2320.